



National
Defence

Defense
nationale

UNCLASSIFIED

DRES

SUFFIELD REPORT

NO. 380

UNLIMITED
DISTRIBUTION

HI-6:

A COMPARATIVE STUDY OF VARIOUS SAMPLES (U)

by

J.G. Clement, P.A. Lockwood and H.G. Thompson

Project No. 13D20

December 1983



DEFENCE RESEARCH ESTABLISHMENT SUFFIELD : RALSTON : ALBERTA

WARNING

The use of this information is permitted subject to recognition of proprietary and patent rights.

Canada

UNCLASSIFIED

UNLIMITED
DISTRIBUTION

DEFENCE RESEARCH ESTABLISHMENT SUFFIELD
RALSTON ALBERTA

SUFFIELD REPORT NO. 380

HI-6:
A COMPARITIVE STUDY OF VARIOUS SAMPLES (U)

by

J.G. Clement, P.A. Lockwood and H.G. Thompson

Project No. 13D20

WARNING

The use of this information is permitted subject to recognition
of proprietary and patent rights .

UNCLASSIFIED

UNCLASSIFIED

UNLIMITED
DISTRIBUTION

DEFENCE RESEARCH ESTABLISHMENT SUFFIELD
RALSTON ALBERTA

SUFFIELD REPORT NO. 380

HI-6:
A COMPARATIVE STUDY OF VARIOUS SAMPLES (U)

by

J.G. Clement, P.A. Lockwood and H.G. Thompson

ABSTRACT

A comparison of the chemical purity, toxicology and efficacy of HI-6 ([[[4-(aminocarbonyl)pyridino]methoxy]methyl]-2-[(hydroxyimino)methyl]-pyridinium dichloride) obtained from various sources was performed. There were no significant differences between HI-6 obtained from either Israel, Yugoslavia, The Netherlands or Canada regarding their efficacy, when combined with atropine, as an antidote of organophosphate poisoning. HI-6 obtained from Great Britain was significantly more toxic and less efficacious than any of the other HI-6 samples. In addition the results of this study showed that there was no significant difference between HI-6 prepared as a laboratory batch and HI-6 prepared commercially with regards to chemical purity, toxicology or efficacy.

UNCLASSIFIED

UNCLASSIFIED

ACKNOWLEDGEMENTS

We would like to thank Drs. H. Edery, L. Leadbeater, B. Bošković and H. Benschop for generous gifts of HI-6 samples. Thanks also go to Drs. K. Simons and C. Briggs of the Department of Pharmacy, University of Manitoba for the HPLC analysis and to Mrs. D. Fehr of the Microanalytical Laboratory of the University of Alberta, Edmonton for microanalyses.

UNCLASSIFIED

UNCLASSIFIED

**DEFENCE RESEARCH ESTABLISHMENT SUFFIELD
RALSTON ALBERTA**

SUFFIELD REPORT NO. 380

**HI-6:
A COMPARATIVE STUDY OF VARIOUS SAMPLES (U)**

by

J.G. Clement, P.A. Lockwood and H.G. Thompson

INTRODUCTION

Atropine plus oxime (PAM, TMB-4 or toxogonin) is an effective treatment for most cases of organophosphate poisoning. In the case of poisoning by soman (pinacolyl methylphosphonofluoridate) however, this treatment is relatively ineffective.

In the past decade new drugs have been synthesized that appear to be very effective against soman poisoning. In particular bispyridinium oximes such as HI-6, HS-6, HGG-12, HGG-42 originating from Professor Hagedorn's laboratory in Freiburg, Germany and BDB-27 from Dr. Binenfeld's group in Belgrade, Yugoslavia have shown potential as new oxime antidotes of organophosphate poisoning.

A great deal of interest has been shown in HI-6. This bispyridinium oxime was found to be an effective antidote with a low toxicity, and relatively inert

UNCLASSIFIED

pharmacologically compared with other bispyridinium compounds such as HGG-12 and HGG-42 (Clement, 1981; Lundy and Tremblay, 1979). Upon examining toxicity data on HI-6 (Table 1) it is apparent that there is a great deal of disparity. This could be the result of differences in either the purity of HI-6 from the various sources or the strain of mouse used in the toxicity studies.

The purpose of this investigation was to examine the chemical purity and the efficacy and toxicity of HI-6 obtained from various sources.

METHODS

Chemistry

Melting points were carried out on a Thomas-Hoover melting point apparatus equipped with a linear temperature programmer. Melting points were uncorrected.

Infrared spectra were obtained using a Beckman 4260 grating spectrophotometer. Samples were run as solid solutions in potassium bromide.

Nuclear magnetic resonance spectra were recorded using a Varian CFT 20 Fourier transform spectrometer with a pulse width of 8 μ sec for ^{13}C and 10 μ sec for ^1H respectively. Samples were run in D_2O at concentrations of 40 mg/mL for ^{13}C and ^1H .

High pressure liquid chromatography (HPLC) was performed using a Waters® HPLC system using the procedure of Benshop *et al.* (1981).

Thin layer chromatography was carried on by the method of Waysbort *et al.* (1981), on aluminum-backed cellulose plates (Merck 5552) using 40:60::1 m HCl:ethanol as solvent and visualization by both Rhodamine B (Stahl, 1969) or iodoplatinic acid (Stahl, 1969).

Toxicology and Efficacy Studies

Male mice (CD-1®, 25 – 30 g) obtained from Canadian Breeding Farm and Laboratories Ltd., St. Constant, Quebec, Canada were used in this study. The animals were acclimatized for at least one week in our animal facilities prior to use. The mice had access to food and water *ad libitum* before and after drug administration. The 24 hr LD_{50} and ED_{50} values and potency ratios were calculated by probit analysis, using the procedure of Finney (1978). All drugs were injected in a volume of 1% of body weight.

In the ED₅₀ studies, the animals were injected with atropine (17.4 mg/kg) + HI-6 i.p., in the same 0.9% saline solution, 5 min prior to receiving sarin (510 µg/kg; s.c.). In the LD₅₀ studies, HI-6 was injected i.p. in 0.9% saline.

Sources of HI-6

Samples of HI-6 were solicited and received from the following individuals: Dr. H. Edery, Israel; Dr. L. Leadbeater, Great Britain; Dr. B. Bošković, Yugoslavia and Dr. H. Benschop, The Netherlands. Upon receipt the samples were stored desicated in the cold (-20°C).

Four Canadian samples of HI-6 were used in this study. All these were prepared by the method of Schoene (1967). DRES-20 was prepared in our laboratories and was recrystallized four times from ethanol/water. DRES-30, -31, -32 were all samples prepared commercially for DRES. DRES-32 was a 10 kg batch of HI-6 that was prepared commercially for DRES and had been recrystallized three times from ethanol/water. DRES-30 was a sample from a commercial preparation which suffered some decomposition during its processing and was recrystallized four times in an attempt to remove all impurities that might be present. DRES-31 was obtained from the same crude product as DRES-30 but it had been recrystallized in a small batch rather than a large one.

Dr. Edery reported that the Israeli sample contained an insoluble impurity and this was confirmed. The insoluble material was not identified.

RESULTS

Chemistry

In appearance samples DRES-20, -30 and -32 were identical, consisting of white chunky crystals. DRES-31 was composed of white needles. The Dutch sample was composed of off-white chunky crystals, while the Yugoslavian sample consisted of yellow chunky crystals. The sample from the UK was a yellow-brown powder. The Israeli sample was an off-white amorphous powder.

All samples melted with decomposition in the range 132 - 138.5°C except for the Israeli sample which melted/decomposed at 174 - 175°C (Table 2). This result identified the sample as anhydrous HI-6 as reported by Binenfeld *et al.* (1978). This fact

pharmacologically compared with other bispyridinium compounds such as HGG-12 and HGG-42 (Clement, 1981; Lundy and Tremblay, 1979). Upon examining toxicity data on HI-6 (Table 1) it is apparent that there is a great deal of disparity. This could be the result of differences in either the purity of HI-6 from the various sources or the strain of mouse used in the toxicity studies.

The purpose of this investigation was to examine the chemical purity and the efficacy and toxicity of HI-6 obtained from various sources.

METHODS

Chemistry

Melting points were carried out on a Thomas-Hoover melting point apparatus equipped with a linear temperature programmer. Melting points were uncorrected.

Infrared spectra were obtained using a Beckman 4260 grating spectrophotometer. Samples were run as solid solutions in potassium bromide.

Nuclear magnetic resonance spectra were recorded using a Varian CFT 20 Fourier transform spectrometer with a pulse width of 8 μ sec for ^{13}C and 10 μ sec for ^1H respectively. Samples were run in D_2O at concentrations of 40 mg/mL for ^{13}C and ^1H .

High pressure liquid chromatography (HPLC) was performed using a Waters* HPLC system using the procedure of Benschop *et al.* (1981).

Thin layer chromatography was carried on by the method of Waysbort *et al.* (1981), on aluminum-backed cellulose plates (Merck 5552) using 40:60::1 m HCl:ethanol as solvent and visualization by both Rhodamine B (Stahl, 1969) or iodoplatinic acid (Stahl, 1969).

Toxicology and Efficacy Studies

Male mice (CD-1*, 25 - 30 g) obtained from Canadian Breeding Farm and Laboratories Ltd., St. Constant, Quebec, Canada were used in this study. The animals were acclimatized for at least one week in our animal facilities prior to use. The mice had access to food and water *ad libitum* before and after drug administration. The 24 hr LD_{50} and ED_{50} values and potency ratios were calculated by probit analysis, using the procedure of Finney (1978). All drugs were injected in a volume of 1% of body weight.

In the ED₅₀ studies, the animals were injected with atropine (17.4 mg/kg) + HI-6 i.p., in the same 0.9% saline solution, 5 min prior to receiving sarin (510 µg/kg; s.c.). In the LD₅₀ studies, HI-6 was injected i.p. in 0.9% saline.

Sources of HI-6

Samples of HI-6 were solicited and received from the following individuals: Dr. H. Edery, Israel; Dr. L. Leadbeater, Great Britain; Dr. B. Bošković, Yugoslavia and Dr. H. Benshop, The Netherlands. Upon receipt the samples were stored desicated in the cold (-20°C).

Four Canadian samples of HI-6 were used in this study. All these were prepared by the method of Schoene (1967). DRES-20 was prepared in our laboratories and was recrystallized four times from ethanol/water. DRES-30, -31, -32 were all samples prepared commercially for DRES. DRES-32 was a 10 kg batch of HI-6 that was prepared commercially for DRES and had been recrystallized three times from ethanol/water. DRES-30 was a sample from a commercial preparation which suffered some decomposition during its processing and was recrystallized four times in an attempt to remove all impurities that might be present. DRES-31 was obtained from the same crude product as DRES-30 but it had been recrystallized in a small batch rather than a large one.

Dr. Edery reported that the Israeli sample contained an insoluble impurity and this was confirmed. The insoluble material was not identified.

RESULTS

Chemistry

In appearance samples DRES-20, -30 and -32 were identical, consisting of white chunky crystals. DRES-31 was composed of white needles. The Dutch sample was composed of off-white chunky crystals, while the Yugoslavian sample consisted of yellow chunky crystals. The sample from the UK was a yellow-brown powder. The Israeli sample was an off-white amorphous powder.

All samples melted with decomposition in the range 132 - 138.5°C except for the Israeli sample which melted/decomposed at 174 - 175°C (Table 2). This result identified the sample as anhydrous HI-6 as reported by Binenfeld *et al.* (1978). This fact

was confirmed by infrared spectroscopy since all samples in the study had identical infrared spectra except for the Israeli sample which had an infrared spectrum identical to that reported by Binenfeld *et al.* (1978) and to an authentic sample of anhydrous HI-6 prepared in our laboratories. Thus, all samples of HI-6 in this study were HI-6 monohydrate except for the Israeli sample.

Thin layer chromatography of all the samples gave a spot for HI-6 in the range R_f 0.462 – 0.469 (Table 2). Only the UK sample showed a second spot when the plates were visualized with rhodamine B. Further analysis by tlc confirmed that this second spot in the UK sample was not due to any of the following compounds, isonicotinamide, pyridine 2-aldoxime, 1,1'-[oxybis(methylene)]bis(2-[(hydroxyimino)methyl]pyridinium dichloride or 1,1'-[oxybis(methylene)]bis(4-aminocarbonyl)pyridinium dichloride.

High pressure liquid chromatography showed no significant impurities in any of the DRES samples or the Israeli sample. Tiny traces of an impurity with a retention time slightly longer than HI-6 were seen in the Dutch and Yugoslavian samples. The sample from the UK contained small amounts of three different materials. None of the impurities were identified.

Nuclear magnetic resonance spectra (both ^1H and ^{13}C) of all samples except the UK sample were identical. The ^{13}C spectrum of the UK sample differed from the other ^{13}C spectra in that the bases of all peaks were considerably broadened and noisy. There were, however, no discrete peaks that could be assigned to impurities. The ^1H spectrum of the UK sample showed similar changes when compared with the ^1H spectra of the other samples. The ^1H spectrum has been previously reported by Binenfeld *et al.* (1978) and the ^{13}C spectrum has been previously reported by Waysbort *et al.* (1981).

Toxicology

Table 3 lists the LD_{50} values of the various samples of HI-6 in non-fasted CD-1 mice. The various samples of DRES HI-6 and Netherlands HI-6 did not differ significantly in toxicity, however they were all significantly different (at least $p < 0.05$) from the Yugoslavian and Great Britain HI-6 LD_{50} values. Not enough HI-6 was available to estimate the toxicity of the Israeli HI-6.

In Table 4 the effect of sex and size of mouse on the HI-6 LD_{50} value are shown. The smaller mice (22 g) tended to have a higher LD_{50} value, however when examined

using the potency ratio, the values were not significantly different. Female mice had a significantly ($p < 0.001$) lower LD_{50} value than male mice in the same weight range but was not significantly different from that in larger, older male mice.

Efficacy

Efficacy of the various HI-6 samples in protecting mice against the lethal effects of sarin is presented in Table 5. Sarin was used as the challenge agent since it was found that this was the agent HI-6 was most effective against (Clement, 1983). In addition, since HI-6 ED_{50} vs sarin was small, we could conserve on the amount of HI-6 used in estimating the ED_{50} values.

The ED_{50} values of the four DRES samples (DRES-20, -30, -31 and -32) were not significantly different from one another and were not significantly different from the samples obtained from Israel, Yugoslavia or The Netherlands. The DRES-32 sample proved to be the most efficacious with the Great Britain sample being $6 \times$ less effective than DRES-20 and DRES-32. The Great Britain HI-6 ED_{50} value was significantly different ($0.01 > p < 0.001$) from all other ED_{50} values when examined using the potency ratio test.

DISCUSSION

The results of this study indicate that HI-6 from various sources (Israel, Yugoslavia, The Netherlands and Canada) is very similar in most respects with regards to its chemical properties and its toxicology and efficacy. Only the HI-6 sample from Great Britain was significantly more toxic and considerably less efficacious than HI-6 from other sources.

The variation in the toxicity of HI-6 (as reported in Table 1) is most likely due to strain differences in mice used in toxicity evaluations rather than significant differences in the purity of the material. Due to the marked difference between the efficacy of the sample of HI-6 from Great Britain and that from Canada caution should be exercised in direct comparison of efficacy data. Utilizing the HI-6 from Great Britain, the relative effectiveness of HI-6, compared to other oximes, as an organophosphate poisoning would not probably be lower than that found using an alternate source of HI-6.

Finally, the results demonstrate that the chemical purity, toxicology and efficacy of HI-6 prepared as small laboratory batch compared to the HI-6 prepared commercially were not significantly different.

REFERENCES

- Benschop, H.P., Konings, C.A.G, Kossen, P. and Ligtenstein, D.P.** (1981). Determination of some pyridinium aldoxime compounds by means of ion-pair reversed phase HPCC; applications in biological material. *J. Chromatog.* **225**: 107 - 114.
- Binenfeld, Z. Deljac, V. Maksimović, M., Markov, V. and Rakin, D.** (1978). HI-6 potencijalni antidot u trovanjima visokotoksicnim inhibitorima kolinesterazu. *Zbornik VMA*:15 - 17.
- Bošković, B.** (1979). The influence of 2-/o-Cresyl/-4 H-1:3:2-benzodioxaphosphorin-2-oxide (CBDP) on organophosphate poisoning and its therapy. *Arch. Toxicol.* **42**:207 - 216.
- Clement, J.G.** (1981). Toxicology and Pharmacology of bis-pyridinium oximes. Insight into the mechanism of action vs soman poisoning *in vivo*. *Fundam. Appl. Toxicol.* **1**:193 - 202.
- Clement, J.G.** (1982). Effect of fasting on the acute toxicity of HI-6 and its efficacy in soman poisoned mice. *Fundam. Appl. Toxicol.* **2**:88 - 89.
- Clement, J.G. and Lockwood, P.A.** (1982). HI-6, an oxime which is an effective antidote of soman poisoning: A structure-activity study. *Toxicol. Appl. Pharmacol.* **64**:140 - 146.
- Clement, J.G.** (1983). Efficacy of mono- and bis-pyridinium oximes versus soman, sarin and tabun poisoning in mice. *Fundam. Appl. Toxicol.*, **in press**.
- Finney, D.J.** (1978). Probit Analysis. Cambridge University Press, Cambridge, 3rd edition.
- Kepner, L.A. and Wolthuis, O.L.** (1978). A comparison of the oximes HS-6 and HI-6 in the therapy of soman intoxication in rodents. *Eur. J. Pharmacol.* **48**:377 - 382.
- Lundy, P.M. and Tremblay, K.P.** (1979). Ganglion blocking properties of some bispyridinium soman antagonists. *Eur. J. Pharmacol.* **60**:47 - 53.

REFERENCES (Cont'd)

- Maksimović, M., Bošković, B., Radović, L., Tadić, V., Deljac, V. and Binenfeld, Z.** (1980). Antidotal effects of bispyridinium-2-monooxime carbonyl derivatives in intoxications with highly toxic organophosphorus compounds. *Acta Pharm. Jugosl.* **30**:151 - 160.
- Schoene, K.** (1967). Darstellung und Untersuchung neuer Acetylcholinesterase Reaktivatoren. Thesis. University of Freiburg.
- Stahl, E.** (1969). Thin Layer Chromatography. Springer-Verlag, Berlin.
- Waysbort, D., Balderman, D. and Amitai, G.** (1981). Carbon-13 NMR Characterization of the Bispyridinium Oximes, Toxogonin, HS-3, HS-6 and HI-6. *Org. Mag. Resonance* **16**:7 - 10.
- Wilhelm, K., Fajdetić, A., Deljac, V. and Binenfeld, Z.** (1979). Protective effect of dextimide and HI-6 in poisoning with highly toxic organophosphorus compounds. *Arch. hig. rada. toksikol.* **30**:147 - 151.

UNCLASSIFIED

Table 1
Toxicity of HI-6 in Mice

LD ₅₀ (mg/kg; i.p.)	Strain	Sex	Reference
390	Albino	M	Bošković, 1979
295	CC57	F	Kepner and Wolthuis, 1978
224	Albino	M	Wilhelm <i>et al.</i> , 1979
660	CD-1®	M	Clement, 1982
550	CD-1®	M	Clement, 1982
514	ALAS	M	Clement, 1981; Clement and Lockwood, 1982
588	CD-1®	M	Clement, 1983
723	Albino	M	Maksimović <i>et al.</i> , 1980

UNCLASSIFIED

UNCLASSIFIED

TABLE 2
A COMPARISON OF VARIOUS SAMPLES OF HI-6*

Test	Sample							
	DRES-20	DRES-30	DRES-31	DRES-32	UK	Holland	Israel	Yugoslavia
Appearance	white, chunky crystals	white, chunky crystals	white needles	white, chunky crystals	brown powder	slightly yellow chunky crystals	off-white powder insoluble impurity	yellow chunky crystals
Melting point (°C)	134.5 – 135	132.5 – 134	132 – 133.5	135 – 136	132 – 134	137 – 138.5	174 – 175	134 – 134.5
TLC (Rf)	0.469	0.469	0.469	0.469	0.469 (0.601)	0.462	0.462	0.469
Infrared spectrum	monohydrate	monohydrate	monohydrate	monohydrate	monohydrate	monohydrate	anhydrous	monohydrate
HPLC	no impurity	not done	no impurity	no impurity	3 impurity peaks	trace impurity at longer retention time than HI-6	no impurity	trace impurity at longer retention time than HI-6
NRM ¹ H	as reported	as reported	as reported	as reported	peaks broadened and noisy	as reported	as reported	as reported
NMR ¹³ C	as reported	as reported	as reported	as reported	peaks broadened and noisy	as reported	as reported	as reported
LD ₅₀ (mg/kg)	588 (546 – 632)	577 (555 – 608)	—	561 (536 – 589)	495 (468 – 528)	563 (535 – 592)	—	653 (605 – 688)
ED ₅₀ vs GB (mg/kg)	0.99 (0.43 – 1.66)	1.53 (0.93 – 2.63)	1.72 (0.93 – 2.94)	0.93 (0.45 – 1.48)	6.2 (3.3 – 9.4)	1.38 (0.93 – 1.73)	1.09 (0.55 – 1.78)	1.33 (0.49 – 1.81)

* Summary Table only, for more details see text and other tables.

UNCLASSIFIED

UNCLASSIFIED

Table 3
LD₅₀ Value of Various Samples of HI-6*

HI-6 Sample	LD ₅₀ (mg/kg)	95% Limits
Great Britain	495	(468 - 528)
Yugoslavia	653	(605 - 688)
Netherlands	563	(535 - 592)
DRES-30	577	(555 - 608)
DRES-20	588	(546 - 632)
DRES-32	561	(536 - 589)

* Oxime injected i.p. in 0.9% saline. Volume of injection was 1% of body weight.

UNCLASSIFIED

UNCLASSIFIED

Table 4
Effect of Weight and Sex on the Toxicity of HI-6 (DRES-32)

Average Body Weight (gm)	Sex	LD ₅₀ (mg/kg; 95% limits)
22	M	619 (586 - 660)
30	M	561 (536 - 589)
35	M	578 (544 - 616)
22	F	548 (530 - 565)*

* Significantly different ($p < 0.001$) from male mice weighing 22 g.

UNCLASSIFIED

UNCLASSIFIED

Table 5
ED₅₀ of Various Samples of HI-6
versus Sarin Poisoning in Mice

HI-6 Sample	ED ₅₀ (mg/kg)	95% Limits
Israel	1.09	0.55 - 1.78
Great Britain	6.2	3.3 - 9.4
Yugoslavia	1.33	0.49 - 1.81
Netherlands	1.38	0.93 - 1.73
DRES-31	1.72	0.93 - 2.94
DRES-30	1.53	0.93 - 2.63
DRES-20	0.99	0.43 - 1.66
DRES-32	0.93	0.45 - 1.48

Male non-fasted CD-1 mice (25 - 30 g) were injected i.p. with HI-6 + atropine (17.4 mg/kg) 5 min before receiving sarin (510 µg/kg, s.c.). Mortality was assessed 24 hr after sarin administration.

UNCLASSIFIED

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall document is classified)

1. ORIGINATING ACTIVITY DRES		2a. DOCUMENT SECURITY CLASSIFICATION Unclassified	
3. DOCUMENT TITLE "HI-6: A Comparative Study of Various Samples"		2b. GROUP	
4. DESCRIPTIVE NOTES (Type of report and inclusive dates) SR 380			
5. AUTHOR(S) (Last name, first name, middle initial) J.G. Clement, P.A. Lockwood and H.G. Thompson			
6. DOCUMENT DATE December 1983		7a. TOTAL NO. OF PAGES 16	7b. NO. OF REFS 15
8a. PROJECT OR GRANT NO. 13D20		8b. ORIGINATOR'S DOCUMENT NUMBER(S) SR 380	
9a. CONTRACT NO.		9b. OTHER DOCUMENT NO.(S) (Any other numbers that may be assigned this document)	
10. DISTRIBUTION STATEMENT Unlimited			
11. SUPPLEMENTARY NOTES		12. SPONSORING ACTIVITY	
13. ABSTRACT A comparison of the chemical purity, toxicology and efficacy of HI-6 ([[[4-(aminocarbonyl)pyridino]methoxy)methyl]-2-[(hydroxyimino)methyl]-pyridinium dichloride) obtained from various sources was performed. There were no significant differences between HI-6 obtained from either Israel, Yugoslavia, The Netherlands or Canada regarding their efficacy, when combined with atropine, as an antidote of organophosphate poisoning. HI-6 obtained from Great Britain was significantly more toxic and less efficacious than any of the other HI-6 samples. In addition the results of this study showed that there was no significant difference between HI-6 prepared as a laboratory batch and HI-6 prepared commercially with regards to chemical purity, toxicology or efficacy.			

KEY WORDS

HI-6 ([[[4-(aminocarbonyl)pyridino]methoxy)methyl]-2-[(hydroxyimino)methyl]-pyridinium dichloride)

Oxime

Analysis

Sarin

INSTRUCTIONS

1. **ORIGINATING ACTIVITY** Enter the name and address of the organization issuing the document.
- 2a. **DOCUMENT SECURITY CLASSIFICATION** Enter the overall security classification of the document including special warning terms whenever applicable.
- 2b. **GROUP** Enter security reclassification group number. The three groups are defined in Appendix M of the DRB Security Regulations.
3. **DOCUMENT TITLE** Enter the complete document title in all capital letters. Titles in all cases should be unclassified. If a sufficiently descriptive title cannot be selected without classification, show title classification with the usual one-capital-letter abbreviation in parentheses immediately following the title.
4. **DESCRIPTIVE NOTES** Enter the category of document, e.g. technical report, technical note or technical letter. If appropriate, enter the type of document, e.g. interim, progress, summary, annual or final. Give the inclusive dates when a specific reporting period is covered.
5. **AUTHOR(S)** Enter the name(s) of author(s) as shown on or in the document. Enter last name, first name, middle initial. If military, show rank. The name of the principal author is an absolute minimum requirement.
6. **DOCUMENT DATE** Enter the date (month, year) of Establishment approval for publication of the document.
- 7a. **TOTAL NUMBER OF PAGES** The total page count should follow normal pagination procedures, i.e., enter the number of pages containing information.
- 7b. **NUMBER OF REFERENCES** Enter the total number of references cited in the document.
- 8a. **PROJECT OR GRANT NUMBER** If appropriate, enter the applicable research and development project or grant number under which the document was written.
- 8b. **CONTRACT NUMBER** If appropriate, enter the applicable number under which the document was written.
- 9a. **ORIGINATOR'S DOCUMENT NUMBER(S)** Enter the official document number by which the document will be identified and controlled by the originating activity. This number must be unique to this document.
- 9b. **OTHER DOCUMENT NUMBER(S)** If the document has been assigned any other document numbers (either by the originator or by the sponsor), also enter this number(s).
10. **DISTRIBUTION STATEMENT** Enter any limitations on further dissemination of the document, other than those imposed by security classification, using standard statements such as:
 - (1) "Qualified requesters may obtain copies of this document from their defence documentation center."
 - (2) "Announcement and dissemination of this document is not authorized without prior approval from originating activity."
11. **SUPPLEMENTARY NOTES** Use for additional explanatory notes.
12. **SPONSORING ACTIVITY** Enter the name of the departmental project office or laboratory sponsoring the research and development. Include address.
13. **ABSTRACT** Enter an abstract giving a brief and factual summary of the document, even though it may also appear elsewhere in the body of the document itself. It is highly desirable that the abstract of classified documents be unclassified. Each paragraph of the abstract shall end with an indication of the security classification of the information in the paragraph (unless the document itself is unclassified) represented as (TS), (S), (C), (R), or (U).

The length of the abstract should be limited to 20 single-spaced standard typewritten lines, 7 1/4 inches long.
14. **KEY WORDS** Key words are technically meaningful terms or short phrases that characterize a document and could be helpful in cataloging the document. Key words should be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context.

POOR

QUALITY

ORIGINAL